High Glucose Uptake by Adipocytes in a Type 1 Diabetic Patient with a Partial 'Honeymoon' Period

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Hypoglycaemic episodes and low insulin requirements are frequently seen in the early phase of treatment of Type 1 diabetes mellitus but the mechanism is not clear. We present a diabetic patient with recurrent hypoglycaemia in the early phase of insulin treatment. A very high glucose transport in adipocytes (basal: 176 and insulin stimulated glucose transport 10^{-7} mol l^{-1}: 335 fl $cell^{-1}$ s^{-1}) was found when compared with reference laboratory diabetic patients (basal: 59 ± 10 and insulin 10^{-7} mol l^{-1}: 106 ± 7 fl $cell^{-1}$ s^{-1}, mean ± SE) and with reference laboratory of non-diabetic subjects (basal: 106 ± 6 and insulin 10^{-7} mol l^{-1}: 188 ± 15 fl $cell^{-1}$ s^{-1}). Insulin binding to adipocytes was in the normal range. The patient was studied again 1 year later when the partial clinical remission had disappeared, and the glucose transport in adipocytes had decreased. In conclusion, an increase in glucose uptake by peripheral tissues may be among the mechanisms of the partial 'honeymoon' period of diabetic patients. © 1998 John Wiley & Sons, Ltd.

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Introduction

Severe hypoglycaemic episodes complicate insulin therapy for diabetes in approximately 10 % of patients with Type 1 diabetes mellitus (DM) and has been considered the cause of death in 4 % of a study of nearly 1000 Type 1 DM patients.[1] Low insulin requirements associated with recurrent hypoglycaemia during the early phase of the disease (the 'honeymoon phase') are well described and have been partially attributed to residual beta cell function.[2,3] Furthermore, although it is widely accepted that diabetic patients are insulin resistant,[4–6] this has been related to their hyperglycaemia.[5,6] It has been reported that during the early phase of diabetes treatment, clinical remission is associated with improvement in *in vivo* insulin-mediated glucose disposal.[7]

In this study we present a patient with Type 1 DM of 6 months' duration who was experiencing a partial honeymoon period. To investigate insulin action at a cellular level, insulin binding and glucose transport were studied in her adipocytes. The study was repeated 1 year later after the partial clinical remission had disappeared.

Case Report

A 51-year-old, non-obese female (BMI 22 kg m^{-2}), presented with a 2-week history of weight loss, polyuria, and polydipsia. Upon admission she was dehydrated and drowsy. Severe ketoacidosis was found (plasma glucose 42.2 mmol l^{-1}, arterial pH 6.95 and urine ketones ++). After emergency treatment, metabolic control was quickly achieved. The HbA_{1c} ranged from 5.2 to 5.6 % (normal range: 3.5–6.1 %). A very poor response of C-peptide to i.v. glucagon (1 mg) was documented (from 300 to 367 pmol l^{-1}). Islet cell auto antibodies (ICA) were positives. During the next 6 months, the patient experienced frequent hypoglycaemic episodes (an average of 2 per week) which persisted as the dose of insulin was gradually reduced to 0.25 U kg^{-1} body weight. Considering the possibility of a 'honeymoon' period due to a residual beta-cell function, a new glucagon test was performed. C-peptide secretion was found still to be very low (basal: 211 pmol l^{-1}, and stimulated: 233 pmol l^{-1}) and we studied the insulin binding and the glucose transport in isolated adipocytes obtained from subcutaneous adipose tissue of the gluteal region. During subsequent follow-up, the patient continued to present with hypoglycaemic episodes, but less frequently (1–2 per month). Her HbA_{1c} rose to 6–7 % and her dose of insulin was gradually increased to 0.48 U kg^{-1} body weight. Another adipose biopsy was performed after 1 year.

Adipocytes were isolated by the method described by

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Pedersen *et al.*,[8] and insulin binding was assessed by the method of Sinha *et al.*[9] Glucose transport into adipocytes was determined by measuring the entry of U-[^{14}C]-D-glucose (New Research Products, Dupont de Nemours, GmbH, Bad Homburg, Germany) at tracer concentrations, as described by Kashiwagi *et al.*[10]

The maximal specific insulin binding was 6.0 % and 6.5 %/50 000 cells in the case reported at 6 months and 1.5 years from the onset of the diabetes. These values were within the range of the reference laboratory diabetic patient group (5.2–6.5 %/50 000 cells) and also within the range of the reference laboratory of the non-diabetic control group (5.6–6.7 %/50 000 cells).

Figure 1 shows the results of the glucose transport in adipocytes in the reference group of patients with diabetes (8 Type 1 diabetic patients, age range 18–45 years), in the reference control group (11 women, age range 30–60 years) and in the case reported. There was a three-fold increase in the first study and a two-fold increase in the second study of both basal (176 and 104 fl cell^{-1} s^{-1}, respectively) and insulin-stimulated glucose transport in adipocytes (insulin 10^{-7} mol l^{-1}: 335 and 198 fl cell^{-1} s^{-1}, respectively) compared with the corresponding mean values of the reference laboratory diabetic patients group (basal: 59 ± 10 and insulin 10^{-7} mol l^{-1}: 106 ± 7 fl cell^{-1} s^{-1}). In comparison with the reference laboratory control group (basal: 106 ± 6 and insulin 10^{-7} mol l^{-1}: 188 ± 15 fl cell^{-1} s^{-1}), our patient presented higher basal and insulin-stimulated glucose transport in the first study and normal glucose transport in the second study.

Discussion

The initial course of Type 1 diabetes is poorly understood. During the first months of therapy, 40 to 50 % of patients experience a partial clinical remission and are able to reduce or even discontinue their dose of insulin.[7] During the first 6 months of insulin treatment in our patient, frequent hypoglycaemic episodes occurred despite treatment with a low insulin dose. This partial 'honeymoon' period could not be explained by residual beta cell function, as has been proposed to occur in some diabetic patients.[3,11] Gray *et al.* suggested that a normalization of insulin action following the institution of insulin treatment may also be a mechanism that might explain the clinical manifestations of the 'honeymoon' phenomenon.[12] Our patient presented a high glucose transport in adipocytes, as both basal and insulin-stimulated glucose transport were above the mean + 2SD of a control group, despite normal insulin binding. Thus, the mechanism of the increased insulin-stimulated glucose transport in our patient seems to be beyond the binding of insulin to its receptor. In the study performed 1 year later, when the partial clinical remission had disappeared, both basal and insulin-stimulated glucose transport in adipocytes had decreased, and were within the normal range.

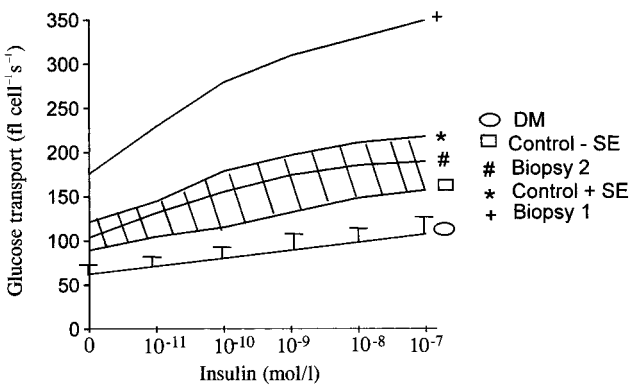

Figure 1. Basal and insulin-stimulated glucose transport in adipocytes; ∗ and □ represent the mean ± SE of the control group; ○ and vertical bars indicate the mean and the SE of the diabetic group; + and # indicate the values of the case report during partial clinical remission (6 months of diabetes) and 1 year later

A tentative explanation for the recurrent hypoglycaemic episodes occurring in the early phase of diabetes treatment in our patient would be an increase in peripheral glucose transport. Although muscle tissue represents the major peripheral target organ of insulin,[13] it has been demonstrated that glucose transport into human adipocytes correlates well with the whole body glucose disposal rate[10,14] and also with glucose uptake by muscle tissue.[15] Data reported in adipocytes from streptozotocin-induced diabetic rats show a decreased insulin-stimulated glucose transport, and insulin treatment not only restored the glucose transport to control levels but also produced a great increase of it.[16] A gradual normalization of the insulin-stimulated glucose transport was observed after some weeks of insulin treatment. These changes were associated with an increase in the protein content and mRNA of the glucose transporter GLUT 4, specific for adipose and muscle.[17]

In patients with Type 1 DM we have previously reported a negative correlation between disease duration and both basal and insulin-stimulated glucose transport in adipocytes. Those patients with a duration of diabetes of longer than 5 years had reduced basal and insulin-stimulated glucose transport.[18] A possible explanation for the deleterious effect of the duration of diabetes on glucose transport may be the action of the circulating glucose levels in the regulation of cellular glucose transport.[19] Euglycaemia ameliorates the characteristic reduction in insulin-stimulated glucose disposal in diabetic patients[2,20] and reversal of hyperglycaemia in diabetic rats with phlorizin normalizes both the *in vivo* insulin-stimulated glucose disposal and restores impaired insulin-stimulated glucose transport in adipocytes.[21] In conclusion, a high glucose transport in peripheral tissues as demonstrated in our case report may contribute to the partial clinical remission that it is frequently observed during the early phase of Type 1 diabetes mellitus.

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References

1. Cryer PE, Gerich JE. Hypoglycaemia in insulin dependent diabetes mellitus: insulin excess and defective glucose counterregulation. In: Rifkin H, Porter D, eds. *Diabetes Mellitus Theory and Practice*, 4th edn. New York: Elsevier, 1990: 526–546.
2. Yki-Järvinen H, Koivisto VA. Insulin sensitivity in newly diagnosed type 1 diabetics after ketoacidosis and after three months of insulin therapy. *J Clin Endocrinol Metab* 1984; **59**: 371–378.
3. Madsbad S. Prevalence of residual B cell function and its metabolic consequences in type I (insulin-dependent) diabetes. *Diabetologia* 1983; **24**: 141–147.
4. DeFronzo RA, Hendler R, Simonson D. Insulin resistance is a prominent feature of insulin-dependent diabetes. *Diabetes* 1982; **31**: 795–801.
5. Leslie R, Taylor R, Pozzilli P. The role of insulin resistance in the natural history of type 1 diabetes. *Diabetic Med* 1997; **14**: 327–331.
6. Yki-Järvinen H, Koivisto VA. Continuous subcutaneous insulin infusion therapy decreases insulin resistance in type 1 diabetes. *J Clin Endocrinol Metab* 1984; **58**: 659–666.
7. Yki-Järvinen H, Koivisto VA. Natural course of insulin resistance in type I diabetes. *N Engl J Med* 1986; **315**: 224–230.
8. Pedersen O, Hjollund E, Beck-Nielsen H, Lindskov HO, Sonne O, Gliemann J. Insulin receptor binding and receptor-mediated insulin degradation in human adipocytes. *Diabetologia* 1981; **20**: 636–641.
9. Sinha MK, Taylor LG, Pories WJ, Flickinger EG, Meellheim D, Atkinson S, *et al*. Long-term effect of insulin on glucose transport and insulin binding in cultured adipocytes from normal and obese humans with and without non-insulin-dependent diabetes. *J Clin Invest* 1987; **80**: 1073–1081.
10. Kashiwagi A, Verso MA, Andrews J, Vasquez B, Reaven G, Foley JE. *In vitro* insulin resistance of human adipocytes isolated from subjects with non-insulin-dependent diabetes mellitus. *J Clin Invest* 1983; **72**: 1246–1254.
11. Ludvigsson J, Heding LG. C-peptide in children with juvenile diabetes. A preliminary report. *Diabetologia* 1976; **12**: 627–630.
12. Gray R, Cowan P, Duncan L, Clarke B. Reversal of insulin resistance in type 1 diabetes following initiation of insulin treatment. *Diabetic Med* 1986; **3**: 18–23.
13. DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP. The effect of insulin on the disposal of intravenous glucose: results from indirect calorimetry and hepatic and femoral venous catheterization. *Diabetes* 1981; **30**: 1000–1007.
14. Ciaraldi TP, Kolterman OG, Olefsky JM. Mechanism of the post-receptor defect in insulin action in human obesity. Decrease in glucose transport system activity. *J Clin Invest* 1981; **68**: 875–880.
15. Susini C, Lavau M. *In vitro* and *in-vivo* responsiveness of muscle and adipose tissue to insulin in rats rendered obese by a high-fat diet. *Diabetes* 1978; **27**: 114–120.
16. Kahn BB, Cushman SW. Mechanism for markedly hyperresponsive insulin-stimulated glucose transport activity in adipose cells from insulin-treated streptozotocin diabetic rats: evidence for increased glucose transporter intrinsic activity. *J Biol Chem* 1987; **262**: 5118–5124.
17. Kahn BB, Charron MJ, Lodish HF, Cushman SW, Flier JS. Differential regulation of two glucose transporters in adipose cells from diabetics and insulin-treated diabetic rats. *J Clin Invest* 1989; **84**: 404–411.
18. Casla A, Arrieta FJ, Gonzalo M, Casanova B, Suarez A, Herrera-Pombo J, Rovira A. Insulin resistance in insulin-dependent diabetic patients is related with duration of the disease (Abstract). *Diabetologia* 1991; **34** (suppl 2): 126 A.
19. Garvey WT, Olefsky JM, Matthaei S, Marshall S. Glucose and insulin co-regulate the glucose transport system in primary cultured adipocytes: a new mechanism of insulin resistance. *J Biol Chem* 1987; **262**: 189–197.
20. Vuorinen-Markkola H, Koivisto VA, Yki-Jarvinen H. Mechanisms of hyperglycemia-induced insulin resistance in whole body and skeletal muscle of type I diabetic patients. *Diabetes* 1992; **41**: 571–580.
21. Rossetti L, Smith D, Shulman GI, Papachristou D, DeFronzo RA. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. *J Clin Invest* 1987; **79**: 1510–1515.

